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(57) Abstract

The present invention relates to pyrazolopyrimidinone derivatives of formula (1), their preparation method and pharmaceutical compositions containing the said derivatives. The compounds have efficacy on the treatment of impotence, one of male sexual dysfunctions with the side effects reduced.

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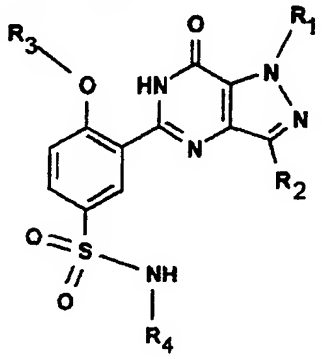
PYRAZOLOPYRIMIDINONE DERIVATIVES FOR THE TREATMENT OF IMPOTENCE

BACKGROUND OF THE INVENTION

The present invention relates to pyrazolopyrimidinone derivatives of the following formula 1, their preparation method and pharmaceutical compositions containing the said derivatives. The compounds have efficacy on the treatment of impotence, one of male sexual dysfunctions with the side effects reduced.

FORMULA 1



Wherein,

R_1 represents hydrogen, alkyl group of C_1-C_6, fluoroalkyl group of C_1-C_3, or cycloalkyl group of C_3-C_6;

R_2 represents hydrogen, substituted or unsubstituted alkyl group of C_2-C_6 , fluoroalkyl group of C_1-C_3, or cycloalkyl group of C_3-C_6;

R_3 represents substituted or unsubstituted alkyl group of C_1-C_6, fluoroalkyl group of C_1-C_6, cycloalkyl group of C_3-C_6, alkenyl group of C_3-C_6, or alkynyl group of C_3-C_6; and

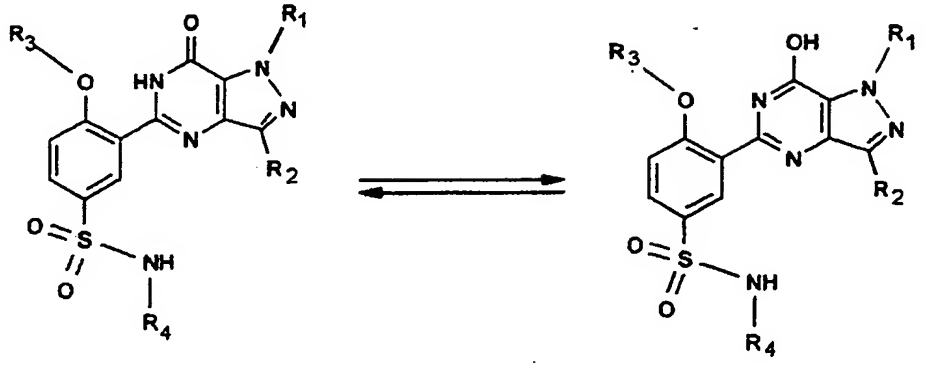
R_4 represents substituted or unsubstituted and linear or branched alkyl group of C_1-C_{10}, substituted or unsubstituted alkenyl group of C_1-C_9, substituted or unsubstituted cycloalkyl group of C_3-C_6, substituted or unsubstituted benzene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazole, oxazole, piperidine, morpholine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl ring.

In case of R_2, R_3 and R_4 being substituted, the substituent is alkyl group of C_1-C_{10}, cycloalkyl group of C_3-C_6, halogen, fluoroalkyl group of C_1-C_6, alkyloxy group of C_1-C_{10}, substituted or unsubstituted benzene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazole, oxazole, piperidine, morpholine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl ring.

The compounds of formula 1 may exist in tautomeric equilibrium represented by the following reaction

scheme 1.

REACTION SCHEME 1



The compounds of formula 1 may contain asymmetric centers and thus they can exist as enantiomers. The present invention includes both mixtures and separate individual isomers.

Male erectile dysfunction is one of the most common sexual dysfunctions in men. Although erectile dysfunction can be primarily psychogenic in origin, it often accompanies chronic illnesses, such as diabetes mellitus, heart disease, hypertension, and a variety of neurological diseases. Its prevalence is strongly related to age, with a estimated prevalence of 2% at age 40 years rising to 25-30% by age of 65. Although no data are available on the prevalence of erectile dysfunction in men aged over 75, it is probably over 50%.

Various treatment options for erectile dysfunction

are available, such as counseling, hormonal therapy, self-injection or transurethral application of vasodilator agents, vacuum devices, prosthesis implantation, and venous/arterial surgery. However, these therapeutic options have several limitations such as side effects, high-cost and low efficacy. Therefore it has called for research efforts to develop new, high effective and simple to use treatment methods, potentially oral medication.

Recently, sildenafil has been developed as a therapeutic agent for male erectile dysfunction by oral administration. Sildenafil is the first in a new class of drugs known as inhibiting phosphodiesterase-5 enzyme distributed specifically in corpus cavernosal tissues and induces relaxation of the corpus cavernosal smooth muscle cells, so that blood flow to the penis is enhanced, leading to an erection. Sildenafil has shown a response rate of around 80% in men with erectile dysfunction of organic cause.

On the other hand, USP 3,939,161 discloses that 1,3-dimethyl-1*H*-pyrazolopyrimidinone derivatives exhibit anticonvulsant and sedative activiity, and also exhibit anti-inflammatory activity and gastric antisecretory activity; EP 201,188 discloses that

5-substituted pyrazolopyrimidinone derivatives have effects of antagonizing adenosine receptor and of inhibiting phosphodiesterase enzymes and can be used for the treatment of cardiovascular disorders such as heart failure or cardiac insufficiency; EP 463,756, EP 526,004, WO 93/6,104 and WO 93/7,149 disclose that pyrazolopyrimidinone derivatives which inhibit c-GMP phosphodiesterase more selectively than c-AMP phosphodiesterase have efficacy on cardiovascular disorders such as angina pectoris, hypertension, heart failure, atherosclerosis, chronic asthma, etc.; and WO 94/28,902, WO 96/16,644, WO 94/16,657 and WO 98/49,166 disclose that the known inhibitors of c-GMP phosphodiesterase including the pyrazolopyrimidinone derivatives of the above mentioned patents can be used for the treatment of male erectile dysfunction.

We, the inventors of the present invention, have investigated to develop the improved therapeutic agent for impotence and synthesized new pyrazolopyrimidinone derivatives which have better potency for the treatment of impotence than that of sildenafil, based on the mechanism of inhibiting phosphodiesterase-5 enzyme. The selectivity over phosphodiesterase-6 distributed in retina and phosphodiesterase-3 distributed in heart, of the compounds of the present invention, is much more

improved, to reduce the side effects. The solubility and the metabolism in the liver, which are very important factor affecting the rate of the absorption when administered orally, of the compounds of the present invention is much more improved.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide pyrazolopyrimidinone derivatives represented by formula 1 and their pharmaceutically acceptable salts.

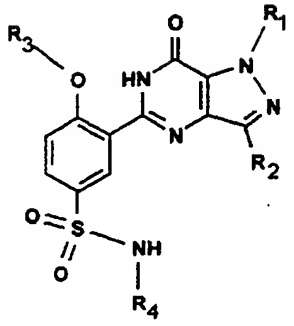
It is another object of the present invention to provide preparation method of the said pyrazolopyrimidinone derivatives.

It is still another object of the present invention to provide pharmaceutical compositions for the treatment of impotence which contain the said pyrazolopyrimidinone derivatives and/or their pharmaceutically acceptable salts as an active ingredient.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides new pyrazolopyrimidinone derivatives of the following formula 1 and their pharmaceutically acceptable salts.

FORMULA 1



Wherein,

R_1 represents hydrogen, alkyl group of C_1-C_6, fluoroalkyl group of C_1-C_3, or cycloalkyl group of C_3-C_6;

R_2 represents hydrogen, substituted or unsubstituted alkyl group of C_2-C_6, fluoroalkyl group of C_1-C_3, or cycloalkyl group of C_3-C_6;

R_3 represents substituted or unsubstituted alkyl group of C_1-C_6, fluoroalkyl group of C_1-C_6, cycloalkyl group of C_3-C_6, alkenyl group of C_3-C_6, or alkynyl group of C_3-C_6; and

R_4 represents substituted or unsubstituted and linear or branched alkyl group of C_1-C_{10}, substituted or unsubstituted alkenyl group of C_1-C_9, substituted or unsubstituted cycloalkyl group of C_3-C_6, substituted or unsubstituted benzene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazole, oxazole,

piperidine, morpholine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl ring.

In case of R_2, R_3 and R_4 being substituted, the substituent is alkyl group of C_1-C_{10}, cycloalkyl group of C_3-C_6, halogen, fluoroalkyl group of C_1-C_6, alkyloxy group of C_1-C_{10}, substituted or unsubstituted benzene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazole, oxazole, piperidine, morpholine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl ring.

In the formula 1, preferably R_1 is alkyl group of C_1-C_3; R_2 is substituted or unsubstituted alkyl group of C_2-C_6; R_3 is substituted or unsubstituted alkyl group of C_2-C_6; and R_4 is substituted or unsubstituted alkyl group of C_1-C_6, substituted or unsubstituted cycloalkyl group of C_3-C_6, substituted or unsubstituted benzene, substituted or unsubstituted pyridine, or substituted or unsubstituted pyrrole. In case of R_2, R_3 and R_4 being substituted, the substituent is preferably halogen, substituted or unsubstituted benzene, substituted or unsubstituted heterocycle selected from the group consisting of pyridine, pyrroldine, piperidine, pyrrole , or substituted or unsubstituted cycloalkyl group of

C_3-C_6.

In the formula 1, more preferably R_4 is substituted alkyl group of C_1-C_6, and the substituent is pyrrolidine.

In particular, the preferable compounds of the present invention are:

1) 5-[2-ethoxy-5-(isopropylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 1);

2) 5-[2-ethoxy-5-(benzylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 2);

3) 5-[2-propyloxy-5-(isopropylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 3);

4) 5-[2-ethoxy-5-(isopropylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 5);

5) 5-[2-ethoxy-5-(propylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 7);

6) 5-[2-ethoxy-5-(propylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 8);

7) 5-[2-ethoxy-5-(butylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 9);

8) 5-[2-ethoxy-5-(2-butylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 10);

9) 5-[2-ethoxy-5-(cyclopropylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 13);

10) 5-[2-ethoxy-5-(cyclopropylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 14);

11) 5-[2-ethoxy-5-(cyclohexylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 19);

12) 5-[2-ethoxy-5-(benzylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 22);

13) 5-[2-propyloxy-5-(benzylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 23);

14) 5-[2-ethoxy-5-(benzylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 24);

15) 5-[2-ethoxy-5-(4-fluorophenylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 26);

16) 5-[2-ethoxy-5-(4-*t*-butylphenylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 28);

17) 5-[2-ethoxy-5-(4-*t*-butylphenylamidosulfonyl) phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 29);

18) 5-[2-ethoxy-5-(4-isopropylphenylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 31);

19) 5-[2-ethoxy-5-(4-fluorophenylamidosulfonyl) phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 33);

20) 5-[2-ethoxy-5-(4-pyridylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 34);

21) 5-[2-propyloxy-5-(4-pyridylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 35);

22) 5-[2-ethoxy-5-(4-pyridylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimi

din-7-one (compound of example 36);

23) 5-[2-ethoxy-5-(4-pyridylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 37);

24) 5-[2-ethoxy-5-(3-pyridylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 38);

25) 5-[2-propyloxy-5-(3-pyridylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 39);

26) 5-[2-ethoxy-5-(3-pyridylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 40);

27) 5-[2-ethoxy-5-(3-pyridylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 41);

28) 5-[2-propyloxy-5-(4-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 44);

29) 5-[2-ethoxy-5-(4-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 46);

30) 5-[2-ethoxy-5-(3-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-

d)pyrimidin-7-one (compound of example 47);

31) 5-[2-ethoxy-5-(3-pyridylmethylamidosulfonyl) phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4 ,3-*d*)pyrimidin-7-one (compound of example 48);

32) 5-[2-propyloxy-5-(3-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4, 3-*d*)pyrimidin-7-one (compound of example 49);

33) 5-[2-ethoxy-5-(2-pyridylmethylamidosulfonyl) phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4 ,3-*d*)pyrimidin-7-one (compound of example 51);

34) 5-[2-propyloxy-5-(2-pyridylmethylamido sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyr azolo(4,3-*d*)pyrimidin-7-one (compound of example 52);

35) 5-[2-propyloxy-5-(1-methyl-3-pyrrolidinylamido sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyr azolo(4,3-*d*)pyrimidin-7-one (compound of example 53);

36) 5-[2-ethoxy-5-(1-methyl-3-pyrrolidinylamido sulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-p yrazolo(4,3-*d*)pyrimidin-7-one (compound of example 54);

37) 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinyl methylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dih ydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 56);

38) 5-[2-ethoxy-5-(1-methyl-2-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 58);

39) 5-[2-propyloxy-5-(1-methyl-3-pyrrolidinyl methylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 60);

40) 5-[2-ethoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 62);

41) 5-[2-propyloxy-5-(1-ethyl-3-pyrrolidinyl methylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 64);

42) 5-[2-ethoxy-5-(1-ethyl-3-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 66);

43) 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 68); and

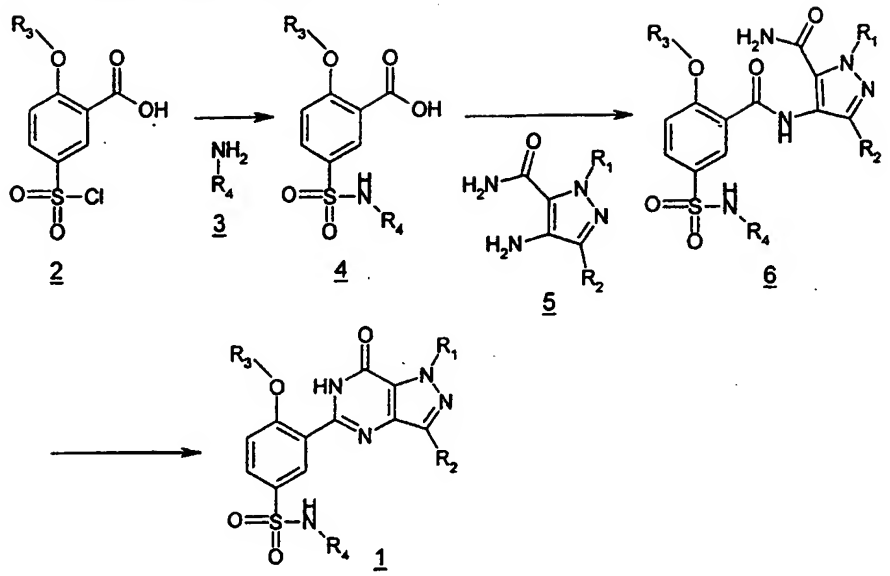
44) 5-[2-ethoxy-5-(1-methyl-2-pyrrolidinylethyl

amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 70).

The compounds of formula 1 according to the present invention can be used in the forms of pharmaceutically acceptable salts, in particular, acid additive salts which are prepared by using pharmaceutically acceptable free acid. Preferred free acids are inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, etc. and organic acids such as citric acid, tartaric acid, acetic acid, lactic acid, maleic acid, fumaric acid, gluconic acid, methanesulfonic acid, glycolic acid, succinic acid, *p*-toluenesulfonic acid, galacturonic acid, embonic acid, glutamic acid, aspartic acid, etc. Also the compounds of formula 1 can be used in the forms of pharmaceutically acceptable metal salts, particularly alkali metal salts such as sodium or potassium salts.

In addition, the present invention provides preparation methods of pyrazolopyrimidinone derivatives of formula 1, represented by the following reaction scheme 2.

REACTION SCHEME 2



Wherein R_1, R_2, R_3 and R_4 are each defined as the formula 1.

The process for preparation according to the present invention comprises the steps of:

1) reacting the chlorosulfonated compound of formula (2) and primary amine (3) under the condition of suitable temperature and suitable solvent to give sulfonamide (4) (step 1);

2) reacting the carboxylic acid (4) prepared in step 1 and pyrazoleamine (5) to give an amide (6) by the known method preparing amide from carboxylic acid and amine (step 2); and

3) cyclizing the amide (6) prepared in step 2 to give the desired compound of formula 1 by the known

cyclization method used for preparation of pyrimidinone (step 3).

In step 1, a little excess of 2 equivalents of amine may be used, or a little excess of 1 equivalent of amine and 1 equivalent of acid scavenger such as tertiary amine are may be used together. The reaction temperature is preferred below 20 °C.

The known method preparing amide from carboxylic acid and amine in step 2 is the process, for example, in which carboxyl group is transformed into activated acid chloride or acid anhydride by using thionyl chloride, pivaloyl chloride, trichlorobenzoyl chloride, carbonyldiimidazole, diphenylphosphinic chloride, etc. and followed by reacting with amine group, or the process using coupling agents such as DCC (1,3-dicyclo hexylcarbodiimide) or EEDQ (*N*-ethoxycarbonyl-2-ethoxy-1,3-dihydroquinoline).

The cyclization process in step 3 may be carried out in the presence of a suitable base and a suitable solvent. Preferred bases which are employed in step 3 are metal alkoxides; metal salts of ammonia; amine; hydrides of alkali metal or alkaline earth metal; hydroxides; carbonates; bicarbonates; and bicyclic amidines such as DBU (1,8-diazabicyclo[5.4.0]undec -7-ene) and DBN (1,5-diazabicyclo[4.3.0]non-5-ene). Preferred solvents which are employed in step 3 are

alcohols such as methanol, ethanol, isopropanol, *t*-butanol, etc.; ethers such as tetrahydrofuran, dimethoxyethane, dioxane, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, chlorobenzene, etc.; acetonitrile; dimethylsulfoxide; dimethylformamide; *N*-methylpyrrolidin-2-one; and pyridine.

In addition, the present invention provides pharmaceutical compositions for the treatment of impotence containing the compounds of formula 1 as an active ingredient.

The present invention provides pharmaceutical formulations which contain, in addition to non-toxic, inert pharmaceutically suitable excipients, one or more compounds according to the present invention, and methods for their preparation.

The compounds of formula 1 according to the present invention can be administered orally or parenterally and be used in general form of pharmaceutical preparation.

The compounds of the present invention can be prepared for oral or parenteral administration by mixing with generally-used fillers, extenders, binders, wetting agents, disintegrating agents, diluents such as surfactants, or excipients.

The present invention also includes pharmaceutical

dosage forms in dosage units. This means that the dosage forms are present in the form of individual parts, for example tablets, capsules, pills, suppositories and ampules. The content of the active compound corresponds to a fraction or a multiple of an individual dose. The dosage units can contain, for example, 1, 2, 3 or 4 times or 1/2, 1/3 or 1/4 of the individual dose. An individual dose preferably contains the amount of active compound which is administered in one application and which usually corresponds to a whole, one half, one third or a quarter of a daily dose.

Non-toxic inert pharmaceutically suitable excipients are to be understood as solid, semi-solid or liquid diluents, fillers and formulation auxiliaries of all types.

Preferred pharmaceutical dosage forms which may be mentioned are tablets, capsules, pills, granules, suppositories, solutions, suspensions and emulsions, pastes, ointments, gels, creams, lotions, powders and sprays.

Solid preparations for oral administration are tablets, pill, powders and capsules, liquid preparations for oral administrations are suspensions, solutions, emulsions and syrups, and the above mentioned preparations can contain various excipients

such as wetting agents, sweeteners, aromatics and preservatives in addition to generally-used simple diluents such as water and liquid paraffin.

Tablets, capsules, pills and granules can contain the active compound or compounds in addition to the conventional excipients, such as (a) fillers and extenders, for example starches, lactose, sucrose, glucose, mannitol and silicic acid, (b) binders, for example carboxymethylcellulose, alginates, gelatine and polyvinylpyrrolidone, (c) humectants, for example glycerol, (d) disintegrating agents, for example agar-agar, calcium carbonate and sodium carbonate, (e) solution retarders, for example paraffin, and (f) absorption enhancers, for example quaternary ammonium compounds, (g) wetting agents, for example cetyl alcohol and glycerol monostearate, (h) adsorbents, for example kaolin and bentonite, and (i) lubricants, for example talc, calcium stearate, magnesium stearate, and solid polyethylene glycols, or mixtures of the substances listed under (a) to (i).

The tablets, capsules, pills and granules can be provided with the conventional coatings, and can also be of a composition such that they release the active compound or compounds only or preferentially in a certain part of the intestinal tract, if appropriate in a delayed manner, examples of embedding compositions

which can be used being polymeric substances and waxes.

If appropriate, the active compound or compounds can also be present in microencapsulated form with one or more of the above mentioned excipients.

Pharmaceutical dosage forms for parenteral administration are injections, suspensions, emulsions, lyophilized formulations and suppositories.

Suppositories can contain, in addition to the active compound or compounds, the customary water-soluble or water-insoluble excipients, for example polyethylene glycols, fats, for example cacao fat, higher esters (for example C_{14}-alcohol with C_{16}-fatty acid), witepsol, macrogol, tween 61, laurin fat and glycerol gelatin or mixtures of these substances.

Ointments, pastes, creams and gels can contain, in addition to the active compound or compounds, the customary excipients, for example animal and vegetable fats, waxes, paraffins, starch, tragacanth, cellulose derivatives, polyethylene glycols, silicones, bentonites, silicic acid, talc and zinc oxide, or mixtures of these substances.

Powders and sprays can contain, in addition to the active compound or compounds, the conventioanl excipients, for example lactose, talc, silicic acid, aluminum hydroxide, calcium silicate and polyamide

powder, or mixtures of these substances. Sprays can additionally contain the conventional propellants, for example chlorofluorohydrocarbons.

Solutions and emulsions can contain, in addition to the active compound or compounds, the conventioanl excipients, such as solvents, solubilizing agents and emulsifiers, for example water, ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethylformamide, oils, in particular cottonseed oil, groundnut oil, corn germ oil, olive oil, castor oil and sesame oil, glycerol, glycerol form alcohol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan, or mixtures of these substances.

For parenteral administration, the solutions and emulsions are also be in a sterile form which is isotonic with blood.

Suspensions can contain, in addition to the active compound or compounds, the conventioanl excipients, such as liquid diluents, for example water, ethyl alcohol and propylene glycol, and suspending agents, for example ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar, tragacanth and ethyl oleate, or

mixtures of these substances.

The pharmaceutical dosage forms mentioned can also contain coloring agents, preservatives and additives which improve the smell and taste, for example peppermint oil and eucalyptus oil, and sweeteners, for example saccharin.

The above mentioned pharmaceutical dosage forms can also contain other pharmaceutically active compounds in addition to the compounds according to the present invention.

The above mentioned pharmaceutical formulations are prepared in the conventioanl method, for example by mixing the active compound or compounds with the excipient or excipients.

The therapeutically active compounds should preferably be present in the abovementioned pharmaceutical dosage forms in a concentration of about 0.1 to 99.5, preferably about 0.5 to 95% by weight of the total mixture.

In general, it has proved advantageous to administer the active compound or compounds according to the present invention in total amounts of about 0.01 to about 100 mg/kg, preferably 0.1 to 30 mg/kg, 1-3 times every 24 hours, if appropriate in the form of several individual doses, to achieve the desired results. However, it may be necessary to properly

deviate from the dosages mentioned, and in particular to do so as a function of the nature and body weight of the object to be treated, of the severity of the disease, of the nature of the formulation and of the route of administration of the medicament and the period or interval within which administration takes place.

Thus in some cases it can suffice to manage with less than the abovementioned amount of active compound, while in other cases the abovementioned amount of active compound must be exceeded. The particular optimum dosage and mode of administration required for the active compounds can be determined by any expert on the basis of his expert knowledge.

The pyrazolopyrimidinone derivatives of formula 1 according to the present invention have more prominent efficacy on the treatment of impotence than sildenafil, an already established therapeutic agent for impotence, based on the mechanism of inhibiting phosphodiesterase-5 enzyme. The selectivities for phosphodiesterase-6 and phosphodiesterase-3, of the compounds according to the present invention, are much better than those of sildenafil, reducing the side effects such as visual disorders or cardiovascular disorders. Furthermore, the solubility in water at pH=2

& 5 is much more improved and the metabolism in rat liver is noticeably decreased in some of the pyrazolopyrimidinone derivatives of the present invention. Therefore the probability of better absorption and better *in vivo* effect can be expected when administered orally compared with sildenafil and the dose of the compound may be reduced.

Practically and presently preferred embodiments of the present invention are illustrative as shown in the following examples.

However, it will be appreciated that those skilled in the art, on consideration of this disclosure, may make modification and improvements within the spirit and scope of the present invention.

The molecular structure of the compounds of formula 1 according to the present invention was identified by IR spectroscopy, UV spectroscopy, NMR spectroscopy, mass spectroscopy and elemental analysis.

EXAMPLES

<Example 1> Preparation of 5-[2-ethoxy-5-(isopropyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one

(Step 1) Preparation of 2-ethoxy-5-(isopropyl amidosulfonyl)benzoic acid

To 1.8 ml of isopropylamine was added 1.9 g of 2-ethoxy-5-chlorosulfonylbenzoic acid in acetone at 0 °C, and the mixture was stirred below 20 °C for 3 hours. Acetone was removed by evaporation, the residue was diluted with ethyl acetate and extracted with aqueous saturated sodium bicarbonate solution. The product was re-extracted with ethyl acetate after acidifying the extracted bicarbonate aqueous fraction with HCl. The extracted organic layer was washed with water and saturated brine, dried over anhydrous $MgSO_4$, and concentrated to give 1.95 g of the desired compound.

NMR($CDCl_3$) : 1.07(d,6H), 1.58(t,3H), 3.48(m,1H), 4.38(q,2H), 4.50(d, 1H), 7.17(d,1H), 8.08(dd,1H), 8.67(d,1H)

(Step 2) Preparation of 4-[2-ethoxy-5-(isopropyl amidosulfonyl)benzamido]-1-methyl-3-propyl-5-carbomoyl pyrazole

To a solution of 1.8 g of 2-ethoxy-5-(isopropyl amidosulfonyl)benzoic acid in dichloromethane were added 0.87 ml of triethylamine and 0.98 ml of 2,4,6-trichlorobenzoyl chloride at 0 °C, and the mixture was stirred at room temperature for 5 hours.

Then to this mixture was added 1-methyl-3-propyl-4-amino-5-carbamoyl pyrazole, and the resulting mixture was stirred. Precipitated crystals were filtered off and the filtrate was diluted with dichloromethane. The organic layer was washed with saturated sodium bicarbonate solution, water and brine in order, dried over anhydrous $MgSO_4$, concentrated and column chromatographed to give 2.0 g of the pure desired compound.

NMR($CDCl_3$) : 0.90(t,3H), 1.03(d,6H), 1.53(t,3H), 1.59(m,2H), 2.50(t, 2H), 3.40(m,1H), 4.00(s,3H), 4.34(q,2H), 5.27(m,1H), 7.10(d,1H), 7.96(dd,1H), 8.68(d,1H), 9.23(br s,1H)

(Step 3) Preparation of 5-[2-ethoxy-5-(isopropyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one

1.9 g of 4-[2-ethoxy-5-(isopropylamidosulfonyl) benzamido]-1-methyl-3-propyl-5-carbamoyl pyrazole was dissolved in 13.5 ml of *t*-butanol, to this solution was added 590 mg of potassium *t*-butoxide, and the mixture was heated to reflux for 20 hours. The reaction mixture was allowed to cool to room temperature, water was added to the mixture, and the conc. HCl was added to adjust the pH to be about 2. The resulting solid was

filtered and washed with water. The filtered solid was dissolved in dichloromethane, and the dichloromethane layer was washed with water and brine, dried over anhydrous $MgSO_4$, concentrated and purified by silica gel column chromatography to give 1.15 g of the pure desired compound.

NMR($CDCl_3$) : 0.99(t,3H), 1.14(d,6H),1.61(t,3H), 1.62(m,2H), 2.89(t,2H), 3.54(m,1H), 4.25(s,3H), 4.34(q,2H), 4.57(d,1H), 7.12(d,1H), 7.96(dd,1H), 8.93 (d,1H), 10.83(br s,1H)

<Example 2> Preparation of 5-[2-ethoxy-5-(benzyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro -7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one

(Step 1) Preparation of 2-ethoxy-5-(benzyl amidosulfonyl)benzoic acid

To 7.4 ml of benzylamine was added 6 g of 2-ethoxy-5-chlorosulfonylbenzoic acid in acetone at 0 °C, and the mixture was stirred below 20 °C for 3 hours. Acetone was removed by evaporation, the residue was diluted with dichloromethane and extracted with saturated sodium bicarbonate solution. The product was re-extracted with dichloromethane after acidifying the extracted aqueous bicarbonate layer with HCl. The saturated brine, dried over anhydrous $MgSO_4$, and

concentrated to give 5.76 g of the desired compound.

NMR($CDCl_3$) : 1.58(t,3H), 4.16(d,2H), 4.37(q,2H), 5.01(t,1H), 7.07(d,1H), 7.20(m, 5H), 8.00(dd,1H), 8.60(d,1H)

(Step 2) Preparation of 4-[2-ethoxy-5-(benzyl amidosulfonyl)benzamido]-1-methyl-3-isobutyl-5-carbam oyl pyrazole

(Method A) To 0.65 g of 2-ethoxy-5-(benzyl amidosulfonyl)benzoic acid in dichloromethane was added 0.53 ml of thionyl chloride at 0 °C and the mixture was stirred and refluxed for 3 hours. The mixture was allowed to cool and concentrated (reaction mixture 1). To 0.29 g of 1-methyl-3-isobutyl-4-amino-5-carbamoyl pyrazole in dichloromethane were added 0.27 ml of triethylamine and catalytic amount of dimethylaminopyridine, and the mixture was allowed to cool. The above reaction mixture 1 was added to this mixture. The resulting mixture was stirred in ice bath for 30 min and at room temperature for 1 hour. The mixture was diluted with dichloromethane, washed with 1N HCl, saturated sodium bicarbonate solution, water and brine in order, dried over anhydrous $MgSO_4$ and concentrated to 0.82 g of the desired compound.

(Method B) The mixture of 1.0 g of 2-ethoxy-5

-(benzylamidosulfonyl)benzoic acid, 0.59 g of 1-methyl -3-isobutyl-4-amino-5-carbamoyl pyrazole and 0.885 g of EEDQ (2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline) in chloroform was stirred for 3 hours and diluted with chloroform. The organic layer was washed with 1N HCl, saturated sodium bicarbonate solution, water and saturated brine in order, dried over anhydrous $MgSO_4$, concentrated and purified by silica gel column chromatography to 0.92 g of the pure desired compound.

NMR($CDCl_3$) : 0.97(d,6H), 1.55(t,3H), 1.91(m,1H), 2.40(d,2H), 3.98(s,3H), 4.11(d,2H), 4.36(q,2H), 5.55(t,1H), 5.94(br s,1H), 7.08(d,1H). 7.21(m,5H), 7.58(br s,1H), 7.95(dd,1H), 8.69(d,1H), 9.22(br s,1H)

(Step 3) Preparation of 5-[2-ethoxy-5-(benzyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro -7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one

0.82 g of 4-[2-ethoxy-5-(benzylamidosulfonyl)benz amido]-1-methyl-3-isobutyl-5-carbamoyl pyrazole was dissolved in ethanol, to this solution was added 0.173 g of sodium methoxide, and the mixture was heated to reflux for 6 hours. The mixture was allowed to cool to room temperature, water was added to the mixture, and the conc. HCl was added to adjust the pH to be about 2. The resulting precipitate was filtered and washed with

water. The filtered solid was dissolved in dichloromethane, and the dichloromethane layer was washed with water and brine, dried over anhydrous $MgSO_4$ and concentrated to give 0.775 g of the desired compound.

NMR($CDCl_3$) : 0.96(d,6H), 1.62(t,3H), 2.16(m,1H), 2.80(d,2H), 4.18(d,2H), 4.26(s,3H), 4.35(q,2H), 4.83(t,1H), 7.09(d,1H), 7.22(m, 5H), 7.91(dd,1H), 8.89 (d,1H), 10.80(br s,1H)

<Examples 3-70>

As a starting material, suitable amines corresponding each substituent were employed to prepare the compounds of examples 3-70 by the same method to example 1 or 2.

TABLE 1

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
3	methyl	propyl	propyl	2-propyl
	1.00(t,3H), 1.83(m,2H), 3.53(m,1H), 4.39(d,1H), 8.94(d,1H),	1.14(d,6H), 2.06(m,2H), 4.24(t,2H), 7.15(d,1H), 10.90(br s,1H)		1.16(t,3H), 2,93(t,2H), 4.25(s,3H), 7.97(dd,1H),
4	methyl	isobutyl	ethyl	2-propyl
	0.97(d,6H), 2.20(m,1H), 4.26(s,3H), 7.95(dd,1H),	1.14(d,6H), 2,81(d,2H), 4.35(q,2H), 8.92(d,1H),		1.63(t,3H), 3.55(m,1H), 7.11(d,1H), 10.85(br s,1H)

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
5	ethyl	propyl	ethyl	2-propyl
	1.00(t,3H), 1.14(d,6H), 1.49(t,3H), 1.63(t,3H), 1.84(m,2H), 2,92(t,2H), 3.57(m,1H), 4.35(q,2H), 4.35(q,2H), 4.35(d,1H), 7.11(d,1H), 7.94(dd,1H), 8.94(d,1H), 10.85(br s,1H)			
6	methyl	propyl	ethyl	methyl
	1.00(t,3H), 1.62(t,3H), 1.83(m,2H), 2.70(d,3H), 2.90(t,2H), 4.25(s,3H), 4.35(q,2H), 4.50(q,1H), 7.12(d,1H), 7.93(dd,1H), 8.89(d,1H), 10.8(br s,1H)			
7	methyl	propyl	ethyl	propyl
	0.88(t,3H), 1.00(t,3H), 1.50(m,2H), 1.61(t,3H), 1.82(m,2H), 2.94(m,4H), 4.25(s,3H), 4.33(q,2H), 4.50(t,1H), 7.11(d,1H), 7.92(dd,1H), 8.89(d,1H), 10.82(br s,1H)			
8	ethyl	propyl	ethyl	propyl
	0.89(t,3H), 1.01(t,3H), 1.50(t,3H), 1.53(m,2H), 1.63(t,3H), 1.83(m,2H), 2.94(m,4H), 4.35(q,2H), 4.40(t,1H), 4.62(q,2H), 7.12(d,1H), 7.91(dd,1H), 8.92(d,1H), 10.82(br s,1H)			
9	methyl	propyl	ethyl	butyl
	0.88(t,3H), 1.00(t,3H), 1.30(m,2H), 1.44(m,2H), 1.62(t,3H), 1.83(m,2H), 2.94(m,4H), 4.25(s,3H), 4.40(q,2H), 4.50(t,1H), 7.11(d,1H), 7.93(dd,1H), 8.89(d,1H), 11.1(br s, 1H)			
10	methyl	propyl	ethyl	2-butyl
	0.84(t,3H), 1.00(t,3H), 1.09(d,3H), 1.42(m,2H), 1.63(t,3H), 2.91(t,2H), 3.32(m,1H), 4.26(s,3H), 4.35(q,2H), 7.10(d,1H), 7.98(dd,1H), 8.94(d,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
11	methyl	propyl	ethyl	3-pentyl
	0.78(t,6H), 1.62(t,3H), 3.20(m,1H), 7.12(d,1H), 10.83(br s,1H)	1.00(t,3H), 1.87(m,2H), 4.25(s,3H), 7.98(dd,1H),		1.50(m,4H), 2.90(t,2H), 4.35(q,2H), 8.92(d,1H),
12	methyl	propyl	ethyl	t-butyl
	1.00(t,3H), 1.84(m,2H), 4.34(q,2H), 7.96(dd,1H), 8.96(d,1H)	1.27(s,9H), 2.90(t,2H), 4.60(s,3H),		1.62(t,3H), 4.25(s,3H), 7.10(d,1H),
13	methyl	propyl	ethyl	cyclopropyl
	0.65(m,4H), 1.81(m,2H), 4.25(s,3H), 7.96(dd,1H), 8.93(d,1H), 10.83(br s,1H)	1.00(t,3H), 2.32(m,1H), 4.38(q,2H),		1.62 (t,3H), 2.90(t,2H), 7.13(d,1H),
14	ethyl	propyl	ethyl	cyclopropyl
	0.65(m,4H), 1.63(t,3H), 2.92(t,2H), 4.36(q,2H), 4.62(q,2H), 4.89(br s,1H), 7.14(d,1H), 7.97(dd,1H), 8.96(d,1H), 10.82(br s,1H)	1.00(t,3H), 1.84(m,2H),		1.49(4,3H), 2.30(m,1H),
15	methyl	isobutyl	ethyl	cyclopropyl
	0.65(m,4H), 2.18(m,1H), 4.27(s,3H), 7.13(d,1H), 10.82(br s,1H)	0.97(d,6H), 2.31(m,1H), 4.36(q,2H), 7.97(dd,1H),		1.63(t,3H), 2.81(d,2H), 4.88(br s,1H), 8.95(d,1H),
16	methyl	propyl	propyl	cyclopropyl
	0.65(m,4H), 1.84(m,2H), 2.92(t,2H), 4.25(s,3H), 4.25(t,2H), 4.90(br s,1H), 7.15(d,1H), 7.98(dd,1H), 9.00(d,1H), 10.84(br s,1H)	1.00(t,3H), 2.04(m,2H),	1.17 (t,3H),	2.32(m,1H),

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
17	methyl	propyl	ethyl	cyclobutyl
	0.65(m,4H), 1.00(t,3H), 1.17 (t,3H), 1.84(m,2H), 2.04(m,2H). 2.32(m,1H), 2.92(t,2H), 4.25(s,3H), 4.25(t,2H), 4.90(br s,1H), 7.15(d,1H), 7.98(dd,1H), 9.00(d,1H), 10.84(br s,1H)			
18	methyl	propyl	ethyl	cyclopentyl
	1.00(t,3H), 1.56-1.82(m,10H), 1.62(t,3H), 2.91(t,2H), 3.68(m,1H), 4.25(s,3H), 4.40(q,2H), 4.45(d,1H), 7.11(d,1H), 7.94(dd,1H), 8.92(d,1H),10.83(br s,1H)			
19	methyl	propyl	ethyl	cyclohexyl
	1.00(t,3H), 1.19(m,4H), 1.61(t,3H), 1.61(m,4H), 1.84(m,4H), 2.90(t,2H), 3.23(m,1H), 4.25(s,3H), 4.35(q,2H), 4.54(d,2H), 7.09(d,1H), 7.94(dd,1H), 8.91(d,1H), 10.85(br s,1H)			
20	methyl	isobutyl	ethyl	cyclohexyl
	0.97(d,6H), 1.21(m,6H), 1.62(t,3H), 1.61(m,2H), 1.82(m,2H), 2.19(m,1H), 2.80(d,2H), 3.20(m,1H), 4.26(s,3H), 4.35(q,2H), 4.50(d,2H), 7.10(d,1H), 7.97(dd,1H), 8.91(d,1H), 10.82(br s,1H)			
21	methyl	propyl	ethyl	2-tetrafuranylmethyl
	1.01(t,3H), 1.62(t,3H), 1.84(m,6H), 2.92(t,2H), 2.97(m,1H), 3.22(m,1H), 3.73(m,2H), 4.00(m,1H), 4.26(s,3H), 4.35(q,2H), 4.87(m,1H), 7.12(d,1H), 7.91(dd,1H), 8.90 (d,1H), 10.83(br s,1H)			
22	methyl	propyl	ethyl	benzyl
	1.00(t,3H), 1.63(t,3H), 1.85(m,2H), 2.91(t,2H), 4.18(d,2H), 4.26(s,3H), 4.37(q,2H), 4.82(t,1H), 7.09(d,1H), 7.23(m,5H), 7.92(dd,1H), 8.90(d,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
23	methyl	propyl	propyl	benzyl
	1.00(t,3H), 1.16(t,3H), 1.63(m,2H), 2.00(m,2H), 2.91(t,2H), 4.20(m,4H), 4.24(s,3H), 4.81(t,1H), 7.10(d,1H), 7.22(m,5H), 7.96(dd,1H), 8.92(d,1H), 10.84(br s,1H)			
24	ethyl	propyl	ethyl	benzyl
	1.00(t,3H), 1.50(t,3H), 1.63(t,3H), 1.84(m,2H), 2.93(t,2H), 4.18(d,2H), 4.36(q,2H), 4.60(q,2H), 4.65(t,1H), 7.10(d,1H), 7.24(m,5H), 7.94(dd,1H), 8.92(d,1H), 10.81(br s,1H)			
25	methyl	propyl	ethyl	phenyl
	1.02(t,3H), 1.57(t,3H), 1.63(m,2H), 2.90(t,2H), 4.25(s,3H), 4.28(q,2H), 6.70(s,1H), 7.00(d,1H), 7.12(m,5H), 7.74(dd,1H), 8.86(d,1H)			
26	methyl	propyl	ethyl	4-fluorophenyl
	1.00(t,3H), 1.59(t,3H), 1.81(m,2H), 2.87(t,2H), 4.25(s,3H), 4.30(q,2H), 6.79(s,1H), 6.98(m,5H), 7.70(dd,1H), 8.80(d,1H), 10.80(br s,1H)			
27	methyl	propyl	ethyl	4-tolyl
	1.03(t,3H), 1.59(t,3H), 1.64(m,2H), 2.25(s,3H), 2.91(t,2H), 4.25(s,3H), 4.30(q,2H), 6.52(s,1H), 6.99(m,5H), 7.74(dd,1H), 8.87(d,1H)			
28	methyl	propyl	ethyl	4-*t*-butylphenyl
	1.01(t,3H), 1.21(s,9H), 1.59(t,3H), 1.63(m,2H), 2.90(t,2H), 4.25(s,3H), 4.30(q,2H), 6.70(s,1H), 7.00(m,3H), 7.24(d,2H), 7.73(dd,1H), 8.90(d,1H), 10.80(br s,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent: $CDCl_3$ if not specified)			
29	ethyl	propyl	ethyl	4-*t*-butylphenyl
	1.02(t,3H), 1.21(s,9H), 1.48(t,3H), 1.59(t,3H), 1.83(m,2H), 2.92(t,2H), 4.30(q,2H), 4.61(q,2H), 6.62(br s,1H), 7.02(m,3H), 7.24(d,2H), 7.75(dd,1H), 8.91(d,1H), 10.80(br s,1H)			
30	methyl	isobutyl	ethyl	4-*t*-butylphenyl
	0.99(d,6H), 1.21(s,9H), 1.58(t,3H), 2.00(m,1H), 2.81(d,2H), 4.26(s,3H), 4.30(q,2H), 6.57(br s,1H), 7.00(m,3H), 7.24(d,2H), 7.78(dd,1H), 8.96(d,1H), 10.80(br s,1H)			
31	methyl	propyl	ethyl	4-isopropylphenyl
	1.02(t,3H), 1.14(d,6H), 1.57(t,3H), 1.66(m,2H), 2.80(m,1H), 2.90(t,2H), 4.25(s,3H), 4.32(q,2H), 6.59(s,1H), 7.02(m,5H), 7.73(dd,1H), 8.89(d,1H), 10.80(br s,1H)			
32	methyl	propyl	ethyl	3,5-dimethylphenyl
	1.01(t,3H), 1.59(t,3H), 1.64(m,2H), 2.20(s,6H), 2.90(t,2H), 4.25(s,3H), 4.30(q,2H), 6.55(s,1H), 6.72(s,3H), 7.01(d,1H), 7.78(dd,1H), 8.89(d,1H), 10.78(br s,1H)			
33	ethyl	propyl	ethyl	4-fluorophenyl
	1.00(t,3H), 1.49(t,3H), 1.61(t,3H), 1.80(m,2H), 2.89(t,2H), 4.30(q,2H), 4.61(q,2H), 6.72(s,1H), 7.04(m,5H), 7.68(dd,1H), 8.80(d,1H), 10.79(br s,1H)			
34	methyl	propyl	ethyl	4-pyridyl
	(DMSO-d^6) 0.97(t,3H), 1.31(t,3H), 1.72(m,2H), 2.78(t,2H), 4.10(q,2H), 4.12(q,2H), 6.94(d,2H), 7.22(d,1H), 7.86(dd,1H), 7.99(m,3H), 12.10(br s,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
35	methyl	propyl	propyl	4-pyridyl
	(DMSO-d^6) 0.92(t,6H), 1.71(m,4H), 2.76(t,2H), 4.01(t,2H), 4.13(s,3H), 6.93(d,2H), 7.23(d,1H), 7.87(d,1H), 7.98(m,3H), 12.05(br s,1H)			
36	ethyl	propyl	ethyl	4-pyridyl
	(DMSO-d^6) 0.93(t,3H), 1.31(t,3H), 1.38(t,3H), 1.72(m,2H), 2.78(t,2H), 4.14(q,2H), 4.51(q,2H), 6.93(d,2H), 7.22(d,1H), 7.88(dd,1H), 7.97(m,3H), 12.10(br s,1H)			
37	methyl	isobutyl	ethyl	4-pyridyl
	(DMSO-d^6) 0.90(d,6H), 1.30(t,3H), 2.08(m,1H), 2.66(d,2H), 4.13(q,2H), 4.15(s,3H), 6.92(d,2H), 7.21(d,1H), 7.87(dd,1H), 7.94(d,1H), 8.00(d,2H), 12.10(br s,1H)			
38	methyl	propyl	ethyl	3-pyridyl
	(DMSO-d^6) 0.94(t,3H), 1.29(t,3H), 1.72(m,2H), 2.77(t,2H), 4.15(s,3H), 4.15(q,2H), 7.30(m,2H), 7.54(d,1H), 7.64(dd,1H), 7.96(d,1H), 8.25(d,2H), 8.30(s,1H), 10.56(br s,1H) 12.13(br s,1H)			
39	methyl	propyl	propyl	3-pyridyl
	(DMSO-d^6) 0.91(t,3H), 0.93(t,3H), 1.72(m,4H), 2.76(t,2H), 4.04(t,2H), 4.14(s,3H), 7.28(m,2H), 7.54(m,1H), 7.82(dd,1H), 7.95(m,1H), 8.25(d,1H), 8.29(d,1H), 10.55(br s,1H), 12.08(br s,1H)			
40	ethyl	propyl	ethyl	3-pyridyl
	(DMSO-d^6) 0.94(t,3H), 1.29(t,3H), 1.38(t,3H), 1.75(m,2H), 2.80(t,2H), 4.14(q,2H), 4.53(q,2H), 7.27(m,2H), 7.54(d,1H), 7.83(dd,1H), 7.96(m,1H), 8.28(d,2H), 8.30(s,1H), 10.56(br s,1H), 12.13(br s,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent: $CDCl_3$ if not specified)			
41	methyl	isobutyl	ethyl	3-pyridyl
	(DMSO-d^6) 0.91(d,6H), 1.29(t,3H), 2.10(m,1H), 2.66(d,2H), 4.12(q,2H), 4.14(s,3H), 7.28(m,2H), 7.54(d,1H), 7.84(dd,1H), 7.94(d,1H), 8.25(d,2H), 8.29(d,1H), 10.56(br s,1H) 12.12(br s,1H)			
42	methyl	propyl	ethyl	2-pyridyl
	(DMSO-d^6) 0.96(t,3H), 1.32(t,3H), 1.75(m,2H), 2.78(t,2H), 4.15(s,3H), 4.15(q,2H), 6.88(m,1H), 7.18(d,1H), 7.27(dd,1H), 7.73(m,1H), 8.01(m,3H), 12.10(br s,1H)			
43	methyl	propyl	ethyl	4-pyridylmethyl
	0.99(t,3H), 1.62(t,3H), 1.80(m,2H), 2.89(t,2H), 4.23(t,2H), 4.25(s,3H), 4.33(q,2H), 5.19(t,1H), 7.08(d,1H), 7.18(d,2H), 7.89(dd,1H), 8.48(dd,2H), 8.89(d,1H), 10.80(br s,1H)			
44	methyl	propyl	propyl	4-pyridylmethyl
	0.99(t,3H), 1.16(t,3H), 1.62(m,2H), 2.00(m,2H), 2.90(t,2H), 4.21(d,2H), 4.25(s,3H), 4.25(q,2H), 5.20(t,1H), 7.09(d,1H), 7.18(d,2H), 7.89(dd,1H), 8.48(m,2H), 8.90(d,1H), 10.82(br s,1H)			
45	ethyl	propyl	ethyl	4-pyridylmethyl
	(DMSO-d^6) 0.92(t,3H), 1.35(m,6H), 1.73(m,2H), 2.78(t,2H), 4.03(s,2H), 4.18(q,2H), 4.52(q,2H), 7.28(m,3H), 7.87(m,1H), 7.98(m,1H), 8.45(m,2H)			
46	methyl	isobutyl	ethyl	4-pyridylmethyl
	0.97(d,6H), 1.62(t,3H), 2.18(m,1H), 2.80(d,2H), 4.22(d,2H), 4.26(s,3H), 4.35(q,2H), 7.08(d,1H), 7.22(d,2H), 7.89(dd,1H), 8.48(m,2H), 8.89(d,1H), 10.80(br s,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent: $CDCl_3$ if not specified)			
47	methyl	propyl	ethyl	3-pyridylmethyl
	(DMSO-d^6) 0.93(t,3H), 1.33(t,3H), 1.74(m,2H), 2.78(t,2H), 4.02(s,2H), 4.17(s,3H), 4.19(q,2H), 7.31(m,2H), 7.63(m,1H), 7.88(dd,1H), 7.97(d,1H), 8.42(m,2H), 11.82(br s,1H)			
48	methyl	isobutyl	ethyl	3-pyridylmethyl
	0.94(d,6H), 1.60(t,3H), 2.17(m,1H), 2.77(d,2H), 4.20(d,2H), 4.25(s,3H), 4.30(q,2H), 5.42(m,1H), 7.08(d,1H), 7.21(dd,1H), 7.64(m,1H), 7.89(dd,1H), 8.37(d,1H), 8.44(dd,1H), 8.84(d,1H), 10.82(br s,1H)			
49	methyl	propyl	propyl	3-pyridylmethyl
	0.98(t,3H), 1.17(t,3H), 1.79(m,2H), 1.98(m,2H), 2.89(t,2H), 4.23(t,2H), 4.23(d,2H), 4.25(s,3H), 5.14(t,1H), 7.10(d,1H), 7.19(m,1H), 7.65(d,1H), 7.90(dd,1H), 8.38(s,1H), 8.45(d,1H), 8.88(d,1H), 10.85(br s,1H)			
50	methyl	propyl	ethyl	2-pyridylmethyl
	1.01(t,3H), 1.59(t,3H), 1.84(m,2H), 2.92(t,2H), 4.29(s,3H), 4.32(q,2H), 6.03(br s,1H), 7.09(m,3H), 7.54(m,1H), 7.91(dd,1H), 8.40(d,1H), 8.87(d,1H)			
51	methyl	isobutyl	ethyl	2-pyridylmethyl
	0.98(d,6H), 1.59(t,3H), 2.20(m,1H), 2.82(d,2H), 4.25(s,3H), 4.31(q,2H), 4.29(d,2H), 7.12(m,3H), 7.56(m,1H), 7.91(dd,1H), 8.40(d, 1H), 8.87(d,1H)			
52	methyl	propyl	propyl	2-pyridylmethyl
	1.01(t,3H), 1.14(t,3H), 1.84(m,2H), 2.01(m,2H), 2.93(t,2H), 4.20(t,2H), 4.25(s,3H), 4.29(d,2H), 5.98(t,1H), 7.06(d,1H), 7.15(m,2H), 7.56(m,1H), 7.91(dd,1H), 8.40(m,1H), 8.89(d,1H), 10.82(br s,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent: $CDCl_3$ if not specified)			
53	methyl	propyl	propyl	1-methy-3-pyrrolidinyl
	1.00(t,3H), 1.16(t,3H), 1.85(m,4H), 2.04(m,2H), 2.12(m,2H), 2.40(m,1H), 2.51(m,1H), 2.77(m,1H), 2.91(t,2H), 3.95(m,1H), 4.23(q,2H), 4.25(s,3H), 7.11(d,1H), 7.92(dd,1H), 8.89(d,1H)			
54	methyl	isobutyl	ethyl	1-methyl-3-pyrrolidinyl
	0.97(d,6H), 1.62(t,3H), 1.80(m,2H), 2.15(m,3H), 2.25(s,3H), 2.38(m,1H), 2.52(m,1H), 2.75(m,1H), 2.81(d,2H), 3.93(m,1H), 4.26(s,3H), 4.35(q,2H), 7.10(d,1H), 7.94(dd,1H), 8.88(d,1H)			
55	methyl	propyl	ethyl	1-methyl-2-pyrrolidinyl methyl
	1.02(t,3H), 1.63(t,3H), 1.80(m,2H), 1.86(m,2H), 2.20(m,4H), 2.94(t,2H), 2.99(s,3H), 3.38(m,1H), 3.60(m,2H), 3.83(m,1H), 4.27(s,3H), 4.36(q,2H), 7.18(d,1H), 8.00(dd,1H), 8.88(d,1H)			
56	methyl	propyl	propyl	1-methyl-2-pyrrolidinyl methyl
	0.92(t,3H), 1.05(t,3H), 1.60(m,3H), 1.75(m,3H), 1.92(m,2H), 2.06(s,3H), 2.18(m,1H), 2.30(m,1H), 2.82(t,2H), 2.90(m,3H), 4.13(q,2H), 4.16(s,3H), 7.03(d,1H), 7.85(dd,1H), 8.82(d,1H)			
57	ethyl	propyl	ethyl	1-methyl-2-pyrrolidinyl methyl
	1.01(t,3H), 1.49(t,3H), 1.63(t,3H), 1.71(m,4H), 1.84(m,2H), 2.16(s,3H), 2.21(m,1H), 2.31(m,1H), 2.93(t,2H), 3.03(m,3H), 4.35(q,2H), 4.60(q,2H), 7.12(d,1H), 7.94(dd,1H), 8.92(d,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent:$CDCl_3$ if not specified)			
58	methyl	isobutyl	ethyl	1-methyl-2-pyrrolidinyl methyl
	1.00(d,6H), 1.64(t,3H), 1.72(m,4H), 2.18(s,3H), 2.20(m,2H), 2.44(m,1H), 2.83(d,2H), 3.06(m,3H), 4.28(s,3H), 4.38(q,2H), 7.13(d,1H), 7.94(dd,1H), 8.91(d,1H)			
59	methyl	propyl	ethyl	1-methyl-3-pyrrolidinyl methyl
	0.99(t,3H), 1.50(m,1H), 1.60(t,3H), 1.83(m,2H), 1.95(m,1H), 2.22(m,2H), 2.28(s,3H), 2.75(m,1H), 2.88(t,2H), 2.97(d,1H), 3.65(m,1H), 4.24(s,3H), 4.29(q,2H), 7.09(d,1H), 7.90(dd,1H), 8.82(d,1H)			
60	methyl	propyl	propyl	1-methyl-3-pyrrolidinyl methyl
	0.98(t,3H), 1.15(t,3H), 1.45(m,1H), 1.80(m,2H), 2.00(m,3H), 2.20(m,2H), 2.25(s,3H), 2.34(m,2H), 2.70(m,1H), 2.86(t,2H), 2.95(d,2H), 3.62(t,1H), 4.20(q,2H), 4.23(s,3H), 7.09(d,1H), 7.88(dd,1H), 8.81(d,1H)			
61	ethyl	propyl	ethyl	1-methyl-3-pyrrolidinyl methyl
	1.00(t,3H), 1.50(t,3H), 1.50(m,1H), 1.62(t,3H), 1.84(d,2H), 2.00(m,1H), 2.20(m,1H), 2.29(s,3H), 2.37(m,3H), 2.80(m,1H), 2.90(t,2H), 2.99(d,2H), 4.34(q,2H), 4.61(q,2H), 7.10(d,1H), 7.94(dd,1H), 8.87(d,1H)			
62	methyl	isobutyl	ethyl	1-methyl-3-pyrrolidinyl methyl
	0.94(d,6H), 1.50(m,1H), 1.57(t,3H), 1.95(m,1H), 2.15(m,2H), 2.24(s,3H), 2.33(m,3H), 2.70(m,1H), 2.75(d,2H), 2.95(d,2H), 3.61(m,1H), 4.27(s,3H), 4.30(q,2H), 7.07(d,1H), 7.88(dd,1H), 8.77(d,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent: $CDCl_3$ if not specified)			
63	methyl	propyl	ethyl	1-ethyl-3-pyrrolidinyl methyl
	0.99(t,3H), 1.10(t,3H), 1.61(t,3H), 1.82(m,2H), 2.00(m,1H), 2.50(m,7H), 2.89(t,2H), 2.90(m,1H), 3.00(d,2H), 4.25(s,3H), 4.34(q,2H), 7.10(d,1H), 7.92(dd,1H), 8.85(d,1H)			
64	methyl	propyl	propyl	1-ethyl-3-pyrrollidinyl methyl
	0.98(t,3H), 1.07(t,3H), 1.15(t,3H), 1.48(m,1H), 1.82(m,2H), 2.00(m,3H), 2.40(m,5H), 2.75(m,1H), 2.87(t,2H), 2.96(d,2H), 4.21(q,2H), 4.27(s,3H), 7.09(d,1H), 7.88(dd,1H), 8.84(d,1H)			
65	ethyl	propyl	ethyl	1-ethyl-3-pyrrolidinyl methyl
	0.99(t,3H), 1.05(t,3H), 1.48(t,3H), 1.50(m,1H), 1.62(t,3H), 1.82(m,2H), 1.95(m,1H), 2.40(m,6H), 2.80(m,1H), 2.86(t,2H), 2.92(d,2H), 4.33(q,2H), 4.61(q,2H), 7.10(d,1H), 7.91(dd,1H), 8.87(d,1H)			
66	methyl	isobutyl	ethyl	1-ethyl-3-pyrrolidinyl methyl
	0.94(d,6H), 1.05(t,3H), 1.50(m,1H), 1.61(t,3H), 1.93(m,1H), 2.30(m,7H), 2.80(d,2H), 2.82(m,1H), 2.99(d,2H), 4.26(s,3H), 4.34(q,2H), 7.10(d,1H), 7.91(dd,1H), 8.86(d,1H)			
67	methyl	propyl	ethyl	1-methyl-2-pyrrolidinyl ethyl
	1.02(t,3H), 1.62(t,3H), 1.85(m,2H), 2.10(m,8H), 2.79(s,3H), 2.93(t,2H), 3.18(m,2H), 3.25(m,1H), 3.65(m,1H), 4.27(s,3H), 4.35(q,2H), 7.15(d,1H), 8.00(dd,1H), 8.86(d,1H)			

TABLE 1 - continued

example	R_1	R_2	R_3	R_4
	NMR data (solvent: $CDCl_3$ if not specified)			
68	methyl	propyl	propyl	1-methyl-2-pyrrolidinyl ethyl
	0.97(t,3H), 1.16(t,3H), 1.58(m,4H), 1.80(m,4H), 2.07(m,3H), 2.28(s,3H), 2.37(m,1H), 2.93(t,2H), 3.10(m,3H), 4.22(q,2H), 4.24(s,3H), 7.11(d,1H), 7.90(dd,1H), 8.88(d,1H)			
69	ethyl	propyl	ethyl	1-methyl-2-pyrrolidinyl ethyl
	1.02(t,3H), 1.51(t,3H), 1.61(m,4H), 1.62(t,3H), 1.86(m,4H), 2.22(m,1H), 2.36(s,3H), 2.50(m,1H), 2.93(t,2H), 3.13(m,3H), 4.36(q,2H), 4.64(q,2H), 7.12(d,1H), 7.96(dd,1H), 8.91(d,1H)			
70	methyl	isobutyl	ethyl	1-methyl-2-pyrrolidinyl ethyl
	0.97(t,3H), 1.50(m,4H), 1.60(t,3H), 1.78(m,2H), 2.12(m,2H), 2.28(s,3H), 2.38(m,1H), 2.80(d,2H), 3.10(m,3H), 4.26(s,3H), 4.35(q,2H), 7.10(d,1H), 7.91(dd,1H), 8.88(d,1H)			

<Experiment 1> Test for a penile erection using rats

In order to confirm the efficacy on impotence of the compounds of formula 1, penile erection test was carried out with the normal rat model based on the methods of Benassi-Benelli *et al.* (*Arch. International de Pharmaco-dynamie et de Therapie.*, **1979**, *242*, 241-247), Islam *et al.* (*J. Ethnopharmacol.*, **1991**, *33*, 67-72) and Heaton *et al.* (*J. Urol.*, **1991**, *145*,

1099-1102).

Pyrazolopyrimidinone derivatives were suspended in 0.5 % methyl cellulose and orally administered to rats with a single dose of 10 mg/kg/10ml. After the administration of the drug, the rats were continously observed in terms of the number of penile erections and the number of genital groomings for 2 hours and the penile erection index (PEI) was calculated. The statistical significance of the differences between groups was calculated using Duncan's multiple comparison by the customary statistics program, Sigma-Stat^{R}. More than three rats were assigned to each group. To the rats of the other two groups were adminstered only the equivalent amount of 0.5% methyl cellulose or 10 mg/kg of sildenafil.citrate, and served as negative and positive control group, respectively.

The penile erection indices in rat model with pyrazolopyrimidinone derivatives of examples 1-70 are listed in the following table 2.

TABLE 2

test group	PEI	genital grooming
control	32.0±23.1	3.8±2.1
1	366.7±38.5	3.0±1.0
2	533.3±305.5	5.7±2.5
3	233.3±152.8	2.7±2.1
4	133.3±57.7	2.3±1.2

TABLE 2 - continued

test group	PEI	genital grooming
5	266.7±57.7	3.3±1.2
6	44.4±38.5	1.3±0.6
7	200.0±0.0	6.7±3.8
8	200.0±100.0	3.0±1.0
9	200.0±100.0	4.7±1.2
10	466.7±305.5	4.0±1.7
11	100±0.0	2.7±2.1
12	22.2±38.5	0.3±0.6
13	300.0±100.0	4.3±1.2
14	233.3±57.7	3.0±1.0
15	111.1±101.8	0.7±0.6
16	100±0	1.7±0.6
17	66.7±66.7	1.0±1.0
18	44.4±38.5	1.3±0.6
19	233.3±57.7	5.0±0.0
20	266.7±57.7	2.3±0.6
21	44.4±38.5	2.3±1.5
22	300.0±200.0	2.7±2.1
23	266.7±57.7	3.0±1.0
24	233.3±230.9	2.7±2.9
25	44.4±38.5	2.0±0.0
26	133.3±133.3	4.0±1.7
27	66.7±66.7	2.7±1.2
28	300.0±100.0	3.0±1.0
29	233.3±152.8	3.0±2.0
30	133.3±57.7	2.3±0.6

TABLE 2 - continued

test group	PEI	genital grooming
31	300.0±0	3.3±0.6
32	66.7±66.7	1.3±1.5
33	233.3±57.7	2.7±0.6
34	166.7±57.7	1.3±0.6
35	200.0±0.0	2.0±0.0
36	200.0±173.2	1.3±0.6
37	166.7±57.7	1.3±0.6
38	233.3±230.9	2.7±2.9
39	166.7±57.7	1.3±1.5
40	177.8±203.7	1.7±1.5
41	177.8±203.7	1.7±1.5
42	33.3±57.7	1.3±1.5
43	11.1±19.3	0.7±0.6
44	166.7±115.5	1.3±0.6
45	22.2±38.5	0.7±1.2
46	200.0±173.2	1.3±0.6
47	200.0±100.0	3.0±1.0
48	166.7±57.7	1.3±0.6
49	200.0±173.2	1.3±0.6
50	44.3±38.5	1.0±0.0
51	233.3±152.8	3.0±2.0
52	233.3±57.7	3.0±1.0
53	300.0±200.0	2.7±2.1
54	233.3±230.9	2.7±2.9
55	350.0±173.2	3.8±1.5
56	200.0±81.7	2.0±0.0

TABLE 2 - continued

test group	PEI	genital grooming
57	131.3±128.1	1.8±1.3
58	275.0±170.8	3.0±1.8
59	150.0±57.7	1.5±0.6
60	300.0±81.7	2.8±0.5
61	25.0±28.9	0.8±0.5
62	200.0±100.0	3.0±1.0
63	12.5±25.0	1.5±0.6
64	175.0±95.7	2.8±0.5
65	93.8±94.4	1.8±1.0
66	175.0±95.7	2.8±0.5
67	75.0±61.2	1.8±1.5
68	233.3±152.8	3.0±2.0
69	225.0±95.7	2.3±1.0
70	175.0±50.0	1.8±0.5
sildenafil	200.0±173.2	3.1±1.2

As a result, the usefulness of the pyrazolopyrimidinone derivatives of the present invention was demonstrated by their higher penile erection index than sildenafil, presently used for the treatment of impotence by oral administration.

<Experiment 2> Test for phosphodiesterase-5 (PDE 5) activity

In order to estimate the extent of inhibition for

PDE 5 activity, of the compounds of formula 1, the following test was carried out.

Phosphodiesterase-5 enzyme (PDE 5) was separated from human corpus cavernosal tissues. About 3 g of this tissue was homogenized with 12 ml of Hepes buffer (20 mM Hepes, 250 mM Sucrose, 1 mM EDTA, 1 mM PMSF, pH 7.2) at 4 °C. The solution was filtered with double-layered gauze and centrifuged (100,000 xg) for 60 min at 4 °C. The supernatant was filtered with 0.2 um filter paper and separated by HPLC (Mono Q anion exchange column) with concentration gradient of 0-500 mM NaCl to elute PDE isozymes. The enzyme activity was measured on the each column fraction by the following process to separate PDE 5 fraction and the inhibition for PDE 5 of the compounds of formula 1 was measured using the fraction.

To 1.5 ml tube were added 100 ul of reaction mixture (15 mM Tris-HCl, 5 mM $MgCl_2$, 0.5 mg/ml BSA, pH 7.4) and the appropriate amount of PDE 5 fraction and PDE inhibitor and the mixture was mixed well. To this solution was added [^{3}H]-cAMP or [^{3}H]-cGMP (500 nM, 2 uCi/ml), the mixture was reacted in the incubator of 30 °C for about 1 hour and the reaction was quenched by putting the tube into boiling water for about 45 seconds to 2 min. Then the tube was chilled in ice bath for about 5 min. To this tube was added snake venom (1

mg/ml, 100 ul) or 5'-nucleotidase (0.1 unit/tube) and the mixture was reacted in incubator of 37 °C for 10 min and chilled in ice bath. 3 times volume of methanol to the resin was added to the anion exchange resin (Bio-Rad resin, AG1-X2, 200-400 mesh) which had been already washed with 0.5 N HCl, H_2O, 0.5 N NaOH, H_2O, 0.5 N HCl and H_2O in order and adjusted to pH 5. Then 1 ml of the pretreated resin was dispensed into the each tube with vortexing. The mixture was left at 4 °C for 15 min with occasional vortexing and centrifuged (10,000 rpm) for about 5 min to sediment the resin. The supernatant (700 ul) was transferred to a liquid scintillation vial, and mixed with 10 ml of scintillation cocktail. After stabilizing the solution by leaving it overnight, the radioactivity of the tube was measured by β-counter.

TABLE 3

test compound	IC_{50} (ng/ml)	test compound	IC_{50} (ng/ml)
sildenafil	7.84±0.32	9	4.78±0.25
1	3.74±0.11	10	1.69±0.08
2	5.33±0.09	13	9.35±0.82
3	2.40±0.32	14	35.4±1.25
5	8.79±0.59	19	2.36±0.08
7	8.97±0.67	22	6.78±0.56
8	11.31±0.98	23	6.31±0.51

TABLE 3 - continued

test compound	IC_{50} (ng/ml)	test compound	IC_{50} (ng/ml)
24	42.6±1.52	52	4.91±0.19
26	36.2±0.98	53	10.23±1.03
28	24.4±1.25	54	19.12±1.45
29	26.8±0.78	55	50.57±1.42
31	15.6±0.85	56	7.13±0.13
33	9.84±0.23	57	16.74±1.26
34	1.61±0.07	58	8.02±0.33
35	0.451±0.01	59	68.29±2.68
36	1.49±0.05	60	17.44±1.92
37	0.433±0.02	61	47.19±1.98
38	3.78±0.09	62	20.95±1.59
39	0.560±0.01	63	49.38±1.43
40	4.20±0.06	64	15.88±1.55
41	1.10±0.05	65	38.48±1.98
44	0.163±0.01	66	18.52±1.39
46	0.597±0.02	67	31.67±1.54
47	1.34±0.09	68	4.57±0.04
48	0.442±0.011	69	16.49±0.88
49	0.149±0.008	70	10.50±0.96
51	0.744±0.008		

As a result, it was demonstrated that the pyrazolopyrimidinone derivatives of the present invention inhibit the phosphodiesterase-5 activity in a concentration of 0.1-50 ng/ml (IC_{50}) and therefore

show prominent efficacy on the treatment of impotence in oral administration.

<Experiment 3> Test for phosphodiesterase-6 (PDE 6) activity

The inhibitor for PDE 5 is known to additionally inhibit PDE 6 distributed in retina, isozyme of PDE 5, and which causes visual disorders. Therefore in order to estimate the extent of inhibition for PDE 6, of the compounds of formula 1, the following test was carried out.

Phosphodiesterase-6 enzyme (PDE 6) was separated from the retina of bullfrogs. The retina was added to Ringer`s solution (105 mM NaCl, 2.5 mM KCl, 2 mM $MgCl_2$, 1 mM $CaCl_2$, 5 mM Glucose, 5 mM $NaHCO_3$, 10 mM Hepes, pH 7.5-7.6) containing 6% Percoll and the solution was shaken. Then the cells were disrupted with syringe pressure and centrifuged (about 10,000 rpm) instantaneously to remove the pigment, and the resulting fraction was used as PDE 6 fraction.

10 ul of reaction mixture (20 mM Tris-HCl, 10 mM $MgCl_2$, 0.5 mg/ml BSA, pH 7.5) was dispensed into each well of microplate, to which were added 10 ul of fraction of PDE 6 and 10 ul of PDE inhibitor and the solution was mixed well. 10 ul of trypsin (about 20-100 ug/ml) was added to the solution, the mixture was

reacted in incubator of 4 °C for 1 hour to activate PDE 6 and the reaction was quenched by adding 10 ul of soybean trypsin inhibitor (6 times higher concentration to the trypsin used). To this mixture was added 10 ul of cyclic nucleotide (generally, 10 mM cGMP was added) and appropriate amount of snake venom or 5'-nucleotidase, and the mixture was reacted in incubator of 37 °C for 20 min. The inorganic phosphate produced by this reaction was measured in absorbance at 700-750 nm by adding 150 ul of molybdate solution (0.4 N H_2SO_4, 0.2% ammonium molybdate, 2% sodium dodesyl sulfate, 2% ascorbic acid) prepared immediately before.

TABLE 4

test compound	IC_{50} (ng/ml)	test compound	IC_{50} (ng/ml)
sildenafil	76.7±1.53	22	>1000
1	47.7±1.56	23	330±10.8
2	>1000	24	583±21.7
3	532±23.6	26	243±8.91
5	4.28±0.14	28	250±11.4
7	57.7±1.25	29	813±37.2
8	20.9±1.56	31	44.3±1.23
9	656±25.8	33	608±9.51
10	10.5±0.56	34	27.4±0.79
13	650±28.4	35	29.1±0.85
14	360±12.3	36	6.04±0.15
19	7.00±0.09	37	3.41±0.11

TABLE 4 - continued

test compound	IC_{50} (ng/ml)	test compound	IC_{50} (ng/ml)
38	679±31.7	57	119.7±7.44
39	28.4±1.0	58	56.1±3.16
40	18.2±0.77	59	168.9±6.82
41	13.6±0.81	60	41.0±1.64
44	21.2±1.59	61	53.3±1.58
46	22.3±0.98	62	75.9±3.17
47	45.4±1.46	63	65.8±1.67
48	27.4±1.73	64	48.9±1.64
49	43.6±2.45	65	58.9±1.74
51	97.3±2.46	66	44.6±2.09
52	>1000	67	163.0±7.13
53	49.4±1.39	68	126.9±8.02
54	73.6±1.19	69	57.5±3.84
55	>1000	70	85.7±4.93
56	71.6±1.85		

As shown in the results, since the 50% inhibition concentration (IC_{50}) for PDE 6 is higher than for phosphodiesterase-5 in some of the pyrazolopyrimidinone derivatives, the probability of visual disorders caused by the compounds of the present invention can be much reduced compared with sildenafil.

<Experiment 4> Test for phosphodiesterase-3 (PDE 3) activity

The inhibitor for PDE 5 may inhibit PDE 3 distributed in heart, isozyme of PDE 5, additionally, which may cause side effects in cardiovascular system. Therefore in order to estimate the extent of inhibition for PDE 3, of the compounds of formula 1, the following test was carried out.

Phosphodiesterase-3 enzyme (PDE 3) was separated from platelets of a rabbit. About 60 ml of blood was collected from a puncture of the abdominal artery of a rabbit in heparinized syringes. Platelet-rich plasma was harvested by centrifugation for 5 min at 450 Xg and further centrifuged for 15 min at 1,200 Xg to precipitate the platelets. The platelets were resuspended in homogenizing buffer (50 mM Tris-HCl, 1 mM $MgCl_2$, pH 7.4), homogenized at 4 °C and ultrasonicated (30 sec/ml). The homogenized solution was centrifuged (105,000 Xg) for 1 hr at 4 °C to obtain the supernatant in which PDE was dissolved. The supernatant was separated by DEAE-cellulose column chromatography (Whatman DE52 bead) by using eluent (50 mM Tris-HCl, 3.75 mM 2-mercaptoethanol, pH 6.0) with concentration gradient of 0-1 M sodium acetate to elute PDE isozymes. The PDE activity was measured on the each column fraction by the following process to separate PDE 3 fraction and the inhibition for PDE 3 of the compounds of formula 1 was measured by using the

fraction.

To 1.5 ml tube containing 100 ul of reaction mixture (15 mM Tris-HCl, 5 mM $MgCl_2$, 0.5 mg/ml BSA, pH 7.4) were added appropriate amount of PDE 3 fraction and PDE inhibitor and the solution was mixed well. After [^{3}H]-cAMP or [^{3}H]-cGMP (500 nM, 2 uCi/ml) was added, the mixture was reacted in incubator of 30 °C for about 1 hour and the reaction was quenched by putting the tube into boiling water for about 45 seconds to 2 min. The tube was chilled in ice bath for about 5 min. To this tube was added snake venom (1 mg/ml, 100 ul) or 5'-nucleotidase (0.1 unit/tube) and the mixture was reacted in incubator of 37 °C for 10 min and chilled in ice bath. 3 times volume of methanol to the resin was added to the anion exchange resin (Bio-Rad resin, AG1-X2, 200-400 mesh) which had been already washed with 0.5 N HCl, H_2O, 0.5 N NaOH, H_2O, 0.5 N HCl and H_2O in order and adjusted to pH 5. Then 1 ml of the pretreated resin was added to the each tube with vortexing. The mixture was left at 4 °C for 15 min with occasional vortexing and centrifuged (10,000 rpm) for about 5 min to sediment the resin. The supernatant (700 ul) was transferred to a liquid scintillation vial, and mixed with 10 ml of scintillation cocktail. After stabilizing the mixture by leaving it overnight, the radioactivity of the tube was measured by β-counter.

TABLE 5

test compound	IC_{50} (ug/ml)	test compound	IC_{50} (ug/ml)
sildenafil	33.9±1.64	52	>100
2	>100	53	>100
3	>100	54	>100
9	>100	56	>100
33	93.7±0.54	57	24.0±0.67
34	86.1±0.21	58	>100
35	>100	59	59.8±3.33
38	97.6±0.09	60	>100
39	20.1±1.84	62	82.6±2.41
41	4.79±0.16	63	26.3±1.06
44	6.27±0.95	64	69.4±2.64
46	>100	65	16.6±0.97
47	10.1±0.56	66	46.7±2.41
48	16.7±1.52	68	36.2±1.58
49	12.5±0.78	69	39.5±1.88
51	>100	70	31.8±1.21

As shown in the results, since the 50% inhibition concentration (IC_{50}) for PDE 3 is higher than for PDE 5 in some of the pyrazolopyrimidinone derivatives, the probability of side effects in cardiovascular system caused by the compounds of the present invention can be much reduced compared with sildenafil.

<Experiment 5> Acute oarl toxicity test in rats

The test for confirming the toxicity of the compounds of formula 1 was carried out as follows.

In this test six-week old SPF SD rats were used, and two rats were assigned to each group. The compounds of examples 1, 2, 3, 5, 7, 8, 9, 10, 13, 14, 19, 22, 23, 24, 26, 28, 29, 31, 33, 34, 35, 36, 37, 38, 39, 40, 41, 44, 46, 47, 48, 49, 51, 52, 53, 54, 56, 58, 60, 62, 64, 66, 68 and 70 were suspended in 0.5% methyl cellulose respectively, and administered orally with single dose of 1 g/kg using a ball-tipped needle. The dosing volume was 10 ml/kg. After the administration, the animals were observed for clinical signs of toxicity or mortality and the body weight changes were measured. All survivors at the end of the observation period underwent laparotomy under ether anesthesia and the blood samples were taken from the abdominal aorta for hematological tests and biochemical analysis. After sacrificing the animals, autopsy was performed for macroscopic observation of the organs and tissues. Tissue samples of vital organs from macroscopic legion were removed and fixed in 10% neutral buffered formalin solution, then processed by standard procedures for histopathology and examined with light microscope. There were no significant clinical symptoms, body weight changes and mortalities. Also in hematology, serum chemistry parameters and macroscopic observation,

no drug-related changes were observed. As a result all the compounds tested did not show toxicity in rats up to 1 g/kg, and the lethal dose (LD_{50}) of oral administration was determined to be over 1 g/kg in rats.

<Experiment 6> Solubility in buffer solution in pH=2&5

In order to evaluate the solubilities in water of the compounds of formula 1 in pH=2 and 5 buffer solutions, the experiment as below was performed.

According to that defined in the Korea Pharmacopoeia, citrate-HCl buffer (pH 2) and citrate-NaOH buffer (pH 5) solutions were added to the powdered compounds of formula 1, respectively. After subsequent severe shaking for 30 sec every 5 min in 20 ∓ 5 °C for 30 min, the level of compounds in the filtrate was measured by high performance liquid chromatography. The results were shown in Table 6.

TABLE 6

test compound	solubility (ug/ml)	
	pH 2	pH 5
sildenafil	1585	480
35	11	1
37	99	7
44	373	1
46	183	0.4

TABLE 6 - continued

test compound	solubility (ug/ml)	
	pH 2	pH 5
48	114	0.3
49	43	0
51	215	1
56	3918	6361
58	3722	9003
60	4497	4923
62	4383	3596
68	5356	14758
70	795	708

As shown in the results, the solubilities in water of the compounds according to the present invention are very high. The solubilities in water at pH 2 and 5 of sildenafil were 1585 and 480 ug/ml, respectively. On the other hand, the solubilities in water of the compounds of the present invention, preferrably of exmaples 56, 58, 60, 62 and 68, were 3722-5356 and 4923-14758 ug/ml at pH 2 and 5, respectively. That is, the solubilities in water of the compounds according to the present invention has been increased to maximum 3.3 and 30.7 times compared with those of sildenafil at pH 2 and 5, respectively.

The solubility in water, in particular in acidic

range of pH, of the compound is the very important factor determining the absorption of the compound in oral administration. Therefore, the better absorption of the compounds according to the present invention are expected in the light of the higer solubility of the compounds in acidic range of pH. Also they have an advantage of reducing the dose in oral administration.

<Experiment 7> Metabolism in rat liver

In order to evaluate the extent of metabolism of the compounds of formula 1, the metabolism in rat liver was studied as below similar to the reported method (C. L. Litterist, E. G. Mimnaugh, R. I. Reagan and T. G. Gram., *Drug. Metabol. Disposit.*, **1975**, *3*, 259-265). In short, the disappearance of compounds after incubation in 9,000 Xg supernatant fraction of rat liver homogenate in the presence of NADPH (reduced nicotinamide adenine dinucleotide phosphate) was evaluated.

First, Sprague-Dawley rat (Korea Experiment Animals, SPF) liver was isolated after perfusion through portal vein with 0.1 M phosphate buffer of pH 7.0 using tissue homogenizer at 4 °C. After

centrifugation at 9,000 Xg for 20 min, the supernatants were collected.

The compound stock solution was spiked (10 ug/ml) into each of the eppendorf tubes containing 1 ml of the mixed solution composing 1 volume of supernatants and 2 volumes of generating solution. The generating solution contains 1 mM NADP, 10 mM glucose-6-phosphate, 50 mM nicotinamide and 5 mM $MgCl_2$ in 0.1 M phosphate buffer of pH 7.0. After vortex-mixing, each test tube was incubated in a water bath kept at 37 °C. After 1 hr, was added acetonitrile to the reaction mixture and centrifuged. 100 ul of aliquot of the supernatant was sampled from each test tube for measuring the remnants by high performance liquid chromatography. The results were shown in Table 7.

TABLE 7

test compound	remnants (%)	test compound	remnants (%)
sildenafil	34.6	51	70.4
35	90.6	56	83.9
37	94.8	58	93.5
44	49.8	60	78.2
46	75.9	62	94.5
48	66.0	68	93.0
49	71.3	70	94.1

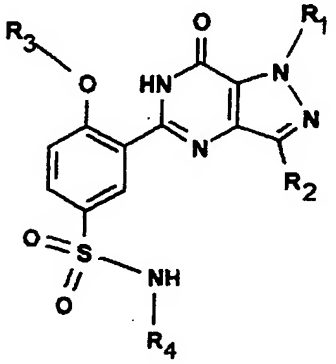
As shown in the results, the extent of metabolism of the compounds in rat liver is noticeably decreased. The remnant (%) of some of the compounds in liver was over 50% while that of sildenafil in liver was about 35%. In particular, the remnant (%) of some of the compounds of the present invention was over 80% and 95% at maximum. That is, it was confirmed that some of the compounds of the present invention were hardly metabolized in liver.

The level of metabolism of the compound in liver is another important factor determining the bioavailability and the in vivo effect, accompanied with the solubility in acidic conditions. The low remnant(%) requires the increase of the dose. Therefore the higher bioavailability and the better in vivo effect of the compounds of the present invention are expected in the light of the less metabolism in liver. Also the compounds of the present invention have an advantage of reducing the dose in oral administration.

What is claimed is :

1. Pyrazolopyrimidinone derivatives represented by the following formula 1 and their pharmaceutically acceptable salts:

FORMULA 1



wherein,

R_1 represents hydrogen, alkyl group of C_1-C_6, fluoroalkyl group of C_1-C_3, or cycloalkyl group of C_3-C_6;

R_2 represents hydrogen, substituted or unsubstituted alkyl group of C_2-C_6 , fluoroalkyl group of C_1-C_3, or cycloalkyl group of C_3-C_6;

R_3 represents substituted or unsubstituted alkyl group of C_1-C_6, fluoroalkyl group of C_1-C_6, cycloalkyl group of C_3-C_6, alkenyl group of C_3-C_6, or alkynyl group of C_3-C_6; and

R_4 represents substituted or unsubstituted and

linear or branched alkyl group of C_1-C_{10}, substituted or unsubstituted alkenyl group of C_1-C_9, substituted or unsubstituted cycloalkyl group of C_3-C_6, substituted or unsubstituted benzene, or substituted or unsubstituted heterocycle selected from the group consisting of pyridine, isoxazole, thiazole, pyrimidine, indan, benzthiazole, pyrazole, thiadiazole, oxazole, piperidine, morpholine, imidazole, pyrrolidine, thienyl, triazole, pyrrole and furyl ring.

2. The pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts according to claim 1, wherein R_1 is alkyl group of C_1-C_3.

3. The pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts according to claim 1, wherein R_2 is substituted or unsubstituted alkyl group of C_2-C_6.

4. The pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts according to claim 1, wherein R_3 is substituted or unsubstituted alkyl group of C_2-C_6.

5. The pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts according to claim 1, wherein R_4 is substituted or unsubstituted alkyl group of C_1-C_6, substituted or unsubstituted cycloalkyl group of C_3-C_6, substituted or unsubstituted benzene, or substituted or unsubstituted pyridine, or substituted or unsubstituted pyrrole.

6. The pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts according to claims 1, 2, 3, 4 or 5, wherein in case of R_2, R_3 and R_4 being substituted, the substituent is halogen, substituted or unsubstituted benzene ring, substituted or unsubstituted heterocycle selected from the group consisting of pyridine, pyrroldine, piperidine, pyrrole, or substituted or unsubstituted cycloalkyl group of C_3-C_6.

7. The pyrazolopyrimidinone derivatives and their pharmaceutically acceptable salts according to claim 1, wherein the compound of the formula 1 is selected from the group consisting of:

1) 5-[2-ethoxy-5-(isopropylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrim

idin-7-one (compound of example 1);

2) 5-[2-ethoxy-5-(benzylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 2);

3) 5-[2-propyloxy-5-(isopropylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 3);

4) 5-[2-ethoxy-5-(isopropylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 5);

5) 5-[2-ethoxy-5-(propylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 7);

6) 5-[2-ethoxy-5-(propylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 8);

7) 5-[2-ethoxy-5-(butylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 9);

8) 5-[2-ethoxy-5-(2-butylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 10);

9) 5-[2-ethoxy-5-(cyclopropylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyri

midin-7-one (compound of example 13);

10) 5-[2-ethoxy-5-(cyclopropylamidosulfonyl) phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 14);

11) 5-[2-ethoxy-5-(cyclohexylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 19);

12) 5-[2-ethoxy-5-(benzylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 22);

13) 5-[2-propyloxy-5-(benzylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 23);

14) 5-[2-ethoxy-5-(benzylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 24);

15) 5-[2-ethoxy-5-(4-fluorophenylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 26);

16) 5-[2-ethoxy-5-(4-*t*-butylphenylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 28);

17) 5-[2-ethoxy-5-(4-*t*-butylphenylamidosulfonyl) phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-

d)pyrimidin-7-one (compound of example 29);

18) 5-[2-ethoxy-5-(4-isopropylphenylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 31);

19) 5-[2-ethoxy-5-(4-fluorophenylamidosulfonyl) phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 33);

20) 5-[2-ethoxy-5-(4-pyridylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 34);

21) 5-[2-propyloxy-5-(4-pyridylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 35);

22) 5-[2-ethoxy-5-(4-pyridylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 36);

23) 5-[2-ethoxy-5-(4-pyridylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 37);

24) 5-[2-ethoxy-5-(3-pyridylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 38);

25) 5-[2-propyloxy-5-(3-pyridylamidosulfonyl) phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-

d)pyrimidin-7-one (compound of example 39);

26) 5-[2-ethoxy-5-(3-pyridylamidosulfonyl)phenyl]-1-ethyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 40);

27) 5-[2-ethoxy-5-(3-pyridylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 41);

28) 5-[2-propyloxy-5-(4-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 44);

29) 5-[2-ethoxy-5-(4-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 46);

30) 5-[2-ethoxy-5-(3-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 47);

31) 5-[2-ethoxy-5-(3-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 48);

32) 5-[2-propyloxy-5-(3-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 49);

33) 5-[2-ethoxy-5-(2-pyridylmethylamidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-pyrazolo(4

,3-*d*)pyrimidin-7-one (compound of example 51);

34) 5-[2-propyloxy-5-(2-pyridylmethylamido sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyr azolo(4,3-*d*)pyrimidin-7-one (compound of example 52);

35) 5-[2-propyloxy-5-(1-methyl-3-pyrrolidinylamido sulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7*H*-pyr azolo(4,3-*d*)pyrimidin-7-one (compound of example 53);

36) 5-[2-ethoxy-5-(1-methyl-3-pyrrolidinylamido sulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro-7*H*-p yrazolo(4,3-*d*)pyrimidin-7-one (compound of example 54);

37) 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinyl methylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dih ydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 56);

38) 5-[2-ethoxy-5-(1-methyl-2-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro -7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 58);

39) 5-[2-propyloxy-5-(1-methyl-3-pyrrolidinyl methylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dih ydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 60);

40) 5-[2-ethoxy-5-(1-methyl-3-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro

-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 62);

41) 5-[2-propyloxy-5-(1-ethyl-3-pyrrolidinyl methylamidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dih ydro-7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 64);

42) 5-[2-ethoxy-5-(1-ethyl-3-pyrrolidinylmethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro -7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 66);

43) 5-[2-propyloxy-5-(1-methyl-2-pyrrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-propyl-1,6-dihydro-7 *H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 68); and

44) 5-[2-ethoxy-5-(1-methyl-2-pyrrolidinylethyl amidosulfonyl)phenyl]-1-methyl-3-isobutyl-1,6-dihydro -7*H*-pyrazolo(4,3-*d*)pyrimidin-7-one (compound of example 70).

8. A process for preparation of pyrazolopyrimidinone derivatives of claim 1 which comprises the steps of:

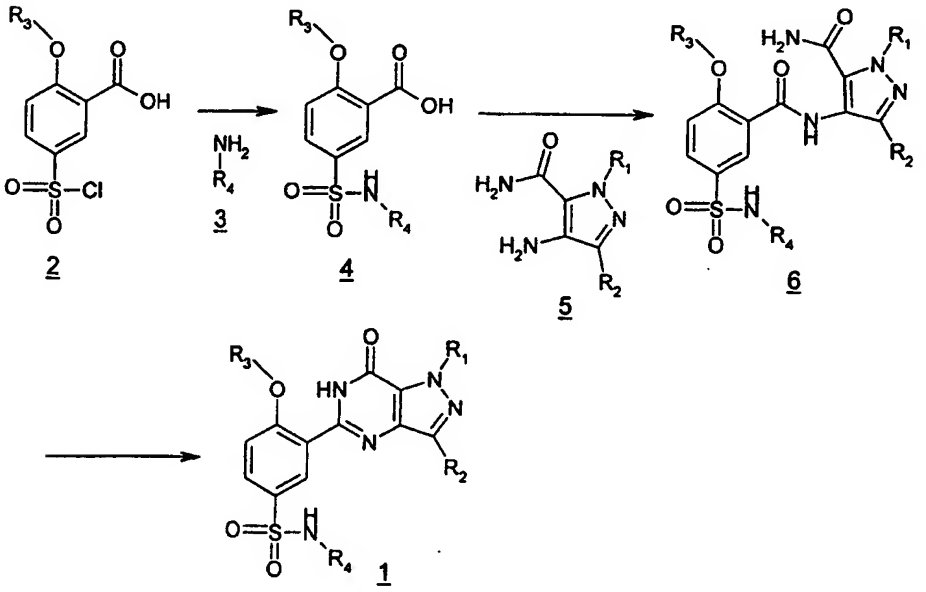
1) reacting the chlorosulfonated compound of formula (2) and primary amine (3) in condition of

suitable temperature and suitable solvent to give sulfoneamide (4) (step 1);

2) reacting the carboxylic acid (4) prepared in step 1 and pyrazoleamine (5) to give an amide (6) by the already established method preparing amide from carboxylic acid and amine (step 2); and

3) cyclizing the amide (6) prepared in step 2 to give the desired compound of formula 1 by the known cyclization reaction used for preparation of pyrimidinone (step 3).

REACTION SCHEME 2



Wherein R_1, R_2, R_3 and R_4 are each defined as the formula 1.

9. Pharmaceutical compositions for the treatment of impotence which contain pyrazolopyrimidinone derivatives and/or their pharmaceutically acceptable salts of claim 1 as an active ingredient.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 99/00675

A. CLASSIFICATION OF SUBJECT MATTER

IPC[7]: C07D 487/04, A61K 31/519

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[7]: C07D 487/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chemical Abstracts

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, DARC: QUESTEL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96/16657 (PFIZER RESEARCH AND DEVELOPMENT COMPANY, N.V./S.A.), 6 June 1996 (06.06.96); cited in the application; claims.	1-9
A	WO 93/06104 (PFIZER INC.), 1 April 1993 (01.04.93); cited in the application; claims.	1-9
A	EP 463756 (PFIZER INC.), 2 Jan 1992 (02.01.92); cited in the application; claims.	1-9
A	WO 94/28902 (PFIZER INC.), 22 December 1994 (22.12.94), cited in the application; claims.	1-9
A	WO 98/49166 (PFIZER INC.), 5 November 1998 (05.11.98), cited in the application; claims.	1-9

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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„&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
7 January 2000 (07.01.00)	27 March 2000 (27.03.00)

Name and mailing adress of the ISA/AT	Authorized officer
Austrian Patent Office Kohlmarkt 8-10; A-1014 Vienna Facsimile No. 1/53424/535	Müller Telephone No. 1/53424/434

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00675

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
WO	A1	9616657	06-06-1996	CA	AA	2203389	06-06-1996
				EP	A1	793498	10-09-1997
				GB	A0	9423911	11-01-1995
				JP	T2	9512835	22-12-1997
WO	A1	9306104	01-04-1993	GB	A0	9119704	30-10-1991
				PT	A	100862	30-11-1993
DK	T3	463756	25-09-1995	AT	E	121403	15-05-1995
EP	A1	463756	02-01-1992	AU	A1	79155/91	19-03-1992
EP	B1	463756	19-04-1995	AU	B2	626757	06-08-1992
				BR	A	9102560	21-01-1992
				CA	AA	2044748	21-12-1991
				CA	C	2044748	03-02-1998
				CN	A	1057464	01-01-1992
				CN	B	1028758	07-06-1995
				CS	A3	9101876	15-04-1992
				CY	A	1971	05-09-1997
				CZ	B6	279289	12-04-1995
				DE	C0	69108991	24-05-1995
				DE	T2	69108991	31-08-1995
				EG	A	19651	31-10-1995
				ES	T3	2071919	01-07-1995
				FI	A0	913017	19-06-1991
				FI	A	913017	21-12-1991
				FI	B	95132	15-09-1995
				FI	C	95132	27-12-1995
				GB	A0	9013750	08-08-1990
				HK	A	2194/96	03-01-1997
				HU	A0	912061	30-12-1991
				HU	A2	61312	28-12-1992
				IE	B	66040	13-12-1995
				IL	A0	98482	15-07-1992
				IL	A1	98482	27-11-1995
				JP	A2	6041133	15-02-1994
				JP	B4	7121945	25-12-1995
				KR	B1	9406628	23-07-1994
				LU	A9	90360	03-05-1999
				NO	A0	912366	18-06-1991
				NO	A	912366	23-12-1991
				NO	B	178029	02-10-1995
				NO	C	178029	10-01-1996
				NZ	A	238586	26-08-1993
				PL	A1	290721	23-03-1992
				PL	B1	166490	31-05-1995
				PT	A	98011	31-03-1992
				PT	B	98011	30-04-1997
				RU	C1	2047617	10-11-1995
				US	A	5250534	05-10-1993
				US	A	5346901	13-09-1994
				US	A	5719283	17-02-1998
				ZA	A	9104707	24-02-1993
				HU	A3	9500148	28-07-1995
				HU	B3	211646	28-12-1995
WO	A1	9428902	22-12-1994	AT	E	163852	15-03-1998
				AU	A1	67973/94	03-01-1995
				AU	B2	676571	13-03-1997
				CA	AA	2163446	22-12-1994
				CA	C	2163446	07-07-1998
				CN	A	1124926	19-06-1996
				CZ	A3	9503242	17-07-1996
				CZ	B6	284946	14-04-1999
				DE	C0	69408981	16-04-1998
				DE	T2	69408981	02-07-1998
				DK	T3	702555	06-04-1998
				EP	A1	702555	27-03-1996
				EP	B1	702555	11-03-1998
				ES	T3	2113656	01-05-1998
				FI	A	955911	08-12-1995
				FI	A0	955911	08-12-1995
				GB	A0	9311920	28-07-1993
				GR	T3	3026520	31-07-1998
				IL	A0	109873	07-10-1994
				IL	A0	121836	22-02-1998
				IL	A1	109873	27-12-1998
				IL	A1	121836	27-12-1998
				JP	T2	9503996	22-04-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/KR 99/00675

Patent document cited in search report			Publication date	Patent family member(s)			Publication date
				JP	B2	2925034	26-07-1999
				JP	A2	11263728	28-09-1999
				JP	A2	11286444	19-10-1999
				LV	A	12269	20-05-1999
				LV	B	12269	20-08-1999
				NO	A	954757	24-11-1995
				NO	A0	954757	24-11-1995
				NZ	A	266463	24-03-1997
				PL	A1	311948	18-03-1996
				ZA	A	9404018	08-12-1995
WO	A1	9849166	05-11-1998	AP	A0	9801228	30-06-1998
				AU	A1	76445/98	24-11-1998
				EP	A1	977756	09-02-2000
				GB	A0	9708406	18-06-1997
				HR	A1	980222	28-02-1999
				NO	A	995211	25-10-1999
				NO	A0	995211	25-10-1999
				GB	A0	9715380	24-09-1997
				GB	A0	9722954	07-01-1998